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Drugs Used in Hepatitis B

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Abstract
Hepatitis B is an infection of the liver caused by hepatitis B virus (HBV). Hepatitis B is one of the most common cause of chronic liver disease and hepatocellular carcinoma. According to WHO, 650,000 people die each year from the complications of chronic hepatitis B. The spectrum of clinical symptoms of the patient varies in the acute and chronic phases. Vaccination against hepatitis B is the only prevention against the virus. Management for chronic hepatitis B is still limited because there is no drug that can eradicate the bacteria completely. Therapy is indicated in patients with high viral loads in active hepatitis, which is supported by increased serum transaminase or the presence of histopathologic outcomes suggesting inflammation and fibrosis. There are two classes of drugs used to treat chronic hepatitis B, namely the group of direct acting nucleoside / nucleotide analogues (NA) and pegylated interferon alfa (PEG). The goal of therapy is to reduce and maintain the lowest possible HBV DNA concentrations that will later on smear on ALT normalization and histologic improvement.

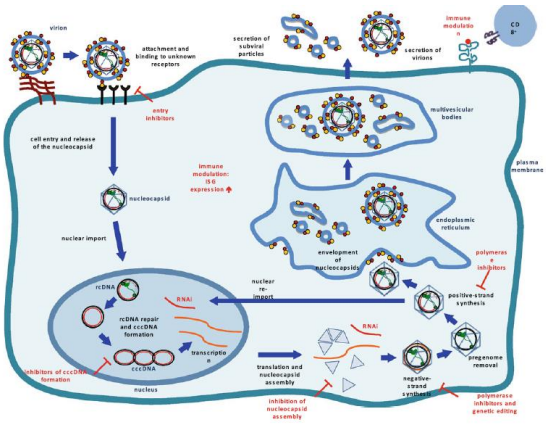
I. INTRODUCTION

Hepatitis B is an infection of the liver caused by hepatitis B virus (HBV). Hepatitis B is one of the most common cause of chronic liver disease and hepatocellular carcinoma worldwide (Antee & Jones, 2014). It is estimated that there are 2 billion people in the world who have a past history or ongoing HBV infection, and 240 million people are carriers of HBV surface antigen. More than 650,000 people die each year from the complications of chronic hepatitis B (WHO, 2015) HBV is transmitted through sexual contact, exposure to percutaneous or perinatal, contacts of injured or open skin, especially in children in endemic areas. The development from acute to chronic in hepatitis B is influenced by the source and time of infection. The highest risk occurs in vertical transmission from mother to child during the perinatal period. In individuals with hepatitis B infection, the outcome were varies withit patient. The patient may had (1) acute hepatitis followed by improvement and clearance of viruses from the body; (2) non-progressive chronic hepatitis; (3) progressive chronic hepatitis developing towards cirrhosis; (4) acute liver failure accompanied by liver necrosis; (5) "healthy" carrier status (asymptomatic) (Theise, 2015)

II. ETHIOLOGY

Hepatitis B virus belongs to the hepadnavirus family and is hepatotropic. The virus is small, 42 nm in diameter, and is also called a Dane particle. The virus consists of a lipid bilayer membrane that incorporates an outer layer composed of small and medium-sized surface proteins. The membrane portion covers the core of the icosahedral nucleocapsid, which consists of 120 dimers of the core protein. Nucleocapsid contains one copy of the DNA genome that binds covalently to viral polymeration proteins. The outer parts of the component are HBsAg and the inside is a HBcAg (core protein) (Morikawa & Sakamoto, 2016; WHO, 2015).

III. PATHOPHYSIOLOGY



Replikasi virus hepatitis B (Grimm et al., 2011)

The viral particles will bind to the hepatocyte-specific receptor preS1. After uncoating the nucleocapsids into the cytoplasm and transporting them to the nucleus, the double-stranded viral relaxed circular DNA (rcDNA) then repaired by viral enzymes and enzymes in cells. From the ligation process of covalent DNA strands will

be produced covalently closed circular DNA (cccDNA). cccDNA virus is a "template" for RNA synthesis where all viral RNAs are transcribed from cccDNA. After transcription, the next process is translation and assembly of virus components. In the cytoplasm, nucleocapsids containing RNA will undergo maturation into DNA via reverse transcription. In the hepatitis B virus cycle, DNA-containing nucleocapsids have two functions. First, they can be imported into the nucleus to form additional cccDNA, or they will be enveloped to be secreted through the endoplasmic reticulum. After budding on the RE lumen, enveloped proteins will be secreted by cells both in the form of noninfectious particles and virions (Grimm, Thimme, & Blum, 2011).

Elimination of the virus by a non-cytopathic mechanism begins a few weeks before the clinical manifestation in the patient appears. Innate and adaptive immune responses to fight HBV involve cytokines, TNF alpha, interferon alfa and beta. After a decrease in viral DNA, cytolytic immune responses, apoptosis of hepatocytes and necrosis occur, along with apparent clinical manifestations in patients and elevated ALT. Infected hepatocytes will be recognized by CD8 cytotoxic T cells, via HLA-1 as the presenting cell antigen, which is then known as the primary mechanism for controlling the virus and causing hepatocyte damage. Cytotoxic T cells will recruit non-specific inflammatory cells by secreting cytokines, which then inject immunological processes that will lead to necro-inflammation. In patients with chronic hepatitis B, responses from both CD4 and CD8 are not able to overcome the virus, which will lead to persistent inflammation (Liaw & Chu, 2009).

Within a few weeks after exposure to the virus (2-10 weeks), HBsAg will be found in the blood, several weeks before an increase in serum aminotransferase. Clinical manifestations will appear after 1-3 months of HBV exposure. HBeAg is found in the acute phase and persists up to a chronic phase and is a marker of active replication of the virus. The discovery of HBsAg and HBeAg signifies high viral replication activity, infection severity and indications for antiviral therapy. Seroconversion of HBeAg to anti HBe suggests improved infection and decreased HBV DNA. The development of chronic hepatitis B disease undergoes several phases, namely immune-tolerant; immune active, immune control, immune escape. This phase is not always sequential and different at different times of the duration (WHO, 2015)

IV. CLINICAL MANIFESTATION

The spectrum of clinical symptoms of the patient varies in the acute and chronic phases. As many as 70% of patients with acute hepatitis B have manifestations of subclinical or aniketeric hepatitis whereas 30% with manifestations of jaundice. Non-specific symptoms that can be found in patients include headaches, myalgia, asthralgia, nausea anorexia that can develop into jaundice within 2 weeks. Patients are also found with pain and discomfort in the stomach, vomiting and diarrhea. Laboratory examination in the acute phase will show increased ALT and AST (ALT is higher than AST) up to 1000-2000 IU / L. In patients undergoing improvement, their value will improve within 1-4 months. However in patients with persistent upsurge of up to 6 months indicates a prognosis of the disease in a chronic direction. In the chronic phase, the manifestations of carrier patients with no clinical symptoms to cirrhosis and malignancy (Lok, 2015).

V. MANAGEMENT THERAPY

a. Prevention of Hepatitis B

Vaccination against hepatitis B is the only prevention against the virus. WHO recommends vaccinations given to all newborns. However, in countries where such vaccines can not be administered, vaccinations are recommended in adults especially those at high risk including health workers, same-sex offenders, free sex practitioners, injecting drug users and families of HBV carriers. Hepatitis B virus tap vaccination has shown a decrease in the incidence of acute hepatitis B and liver carcinoma and the prevalence of chronic hepatitis B infection . (Lok & Negro, 2011). Hepatitis B vaccine is administered intramuscularly in 3 doses at months 0, 1 and month 6 with a dose of 10-20 μg in adults and 5-10 μg in children. The protective response is defined as the presence of an anti-HBs titer (antibody to hepatitis B)> 10 IU / L and achieved at 95% of the recipient. Failure of vaccination occurs in the 2.5-10% recipient because of old age, obesity, have chronic illness, immune-suppression system and technical problems during injection. In non-responsive patients, it is recommended to restart vaccine from the start. Examination of anti-HBs titer should be performed regularly, and booster dosage is performed if the anti-HBs titer is below 10 IU / L. Some studies show that the level of protection from Hepatitis B vaccine can reach 15 years. A common side effect is pain at the injection site. Other side effects include mild malaise, headache, arthralgia, and myalgia (Lok & Negro, Hepatitis B and D, 2011).

b. Management of Acute Hepatitis B

Management in acute hepatitis B patients is supportive according to patient's symptoms. Administration of antiviral does not decrease severity and duration of acute hepatitis treatment. 90-95% will experience

improvement and healing in 6 months characterized by the presence of antibodies against the virus, 5-10% will develop into chronic (Antee & Jones, 2014).

c. Management of Chronic Hepatitis B

Management for chronic hepatitis B is still limited because there is no drug that can eradicate the bacteria completely. The aims of management are sero-conversion of HbeAg, HBV-DNA decline and normalization of liver function tests (LFT). Therapy is indicated in patients with high viral loads in active hepatitis, which is supported by increased serum transaminase or the presence of histopathologic outcomes suggesting inflammation and fibrosis. Drugs will be more effective at lowering viral load in patients with antigen-negative compared to positive e-antigen.

VI. DRUGS FOR CHRONIC HEPATITIS B

There are two classes of drugs used to treat chronic hepatitis B, namely the group of direct acting nucleoside / nucleotide analogues (NA), entecavir, tenofovir, lamivudine, dipovoxil adefovir, telbivudine and pegylated interferon alfa (PEG). NA is preferred because it is well tolerated and can be taken orally. The goal of therapy is to reduce and maintain the lowest possible HBV DNA concentrations that will later on smear on ALT normalization and histologic improvement. The additional goal of therapy is to change HbeAg (+) to anti HBe. Although NA can be discontinued after use of 6-12 after seroconversion, but in patients with recurrent infections (marked by an increase in HBV DNA values), requires longer therapy time.

Table 1. Drugs used in Hepatitis B (Lok, Anna. 2017; Liang et al. 2015.; Terrault, N.A. et al., 2015.; Brunton, L., Chabner, B. & Knollmann, B., 2011)

Class	Drug/Dose	MoA	Potential side effect
Interferon α	Peg-IFN/ A: 180 µg weekly IFN/ C: 6 million IU/m^2	Induce specific Interferon stimulated genes that inhibit HBV transcription or prevent the formation of nucleocapsid or target it for degradation	Flu like symptoms, fatigue, mood disturbance, cytopenias, autoimmune disorders in adult
NRTI	Lamivudine/ A: 100 mg daily C: ≥2yo 3 mg/kg daily, max: 100 mg	potent inhibitor of the DNA polymerase / reverse transcriptase of HBV	Pancretitis, lactic acidosis
	Telbivudine/ A: 600 mg Daily	Telbivudine 5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine 5'-triphosphate into viral DNA causes chain termination	Creatine kinase elevations, myopathy, peripheral neuropathy, lactic acidosis
	Entecavir/ A: 0.5-1 mg daily C: ≥2 yo weight based, 0.5 mg daily (weight > 30 kg)	Entecavir triphosphate competes with endogenous deoxyguanosine triphosphate and inhibits all three activities of the HBV polymerase (reverse transcriptase)	Lactic acidosis
	Adefovir/≥12yo 10 mg Daily	Adefovir is converted by cellular enzymes to the diphosphate, which acts as a competitive inhibitor of viral DNA polymerases and reverse transcriptases with respect to deoxyadenosine triphosphate and also serves as a chain terminator of viral DNA synthesis	Acute renal failure, fanconi syndrome, nephrogenic diabetes insipidus, lactitc acidosis

	Tenofovir disoproxil/≥12yo 300 mg Daily	inhibits reverse transcription of HBV	Nephropathy, fanconi syndrome, osteomalacia, lactic acidosis
	Tenofovir alafenamid /≥12yo 25 mg Daily	inhibits reverse transcription of HBV	Improved side effect profile than tenofovir disoproxil

MoA= Mechanism of action; A= adult; C= children

Table 2. Consideration of therapy (Friedman, L.S., 2017; Lok, Anna. 2017)

Drugs	**Advantage**	**Disadvantage**
Peg-IFN/IFN	Considered in order to avoid long-term therapy with an oral agent; improved survival in up to 40%	Route of adm : parenteral
Lamivudine	More effective than adefovir	Relapse in 15-30% patient; Rate of resistance 70% by 5 years of therapy
Telbivudine	More potent than lamivudine and adefovir	Elevated creatine kinase levels are common
Entecavir	Rarely associated with resistance; histologic improvement is observed in 70% of patients	Side effect: lactic acidosis
Adefovir	Activity against wild-type and lamivudine-resistant HBV	Least potent; Rate of resistance 29% by 5 years of therapy
Tenofovir disoproxil	Used when resistance to a nucleoside analog has developer	Side effect: elevated serum creatinine level, reduced serum phosphate level (Fanconi-like syndrome)
Tenofovir alafenamid	New drug developed to have better safety profile compared with tenofovir disoproxil fumarate	Long term side effect is still unknown

VII. CONCLUSION

Hepatitis B is an infection of the liver caused by hepatitis B virus (HBV) and one of the most common cause of chronic liver disease and hepatocellular carcinoma worldwide The goal of therapy is to reduce and maintain the lowest possible HBV DNA concentrations that will later on smear on ALT normalization and histologic improvement. There are two classes of drugs used to treat chronic hepatitis B, namely the group of direct acting nucleoside / nucleotide analogues (NA) and pegylated interferon alfa (PEG). Each of drug has advantage and disadvantage to be considered during therapy selection.

References

Antee, Q.M. & Jones, D.E.J., 2014. Liver and Biliary Tract Disease. In B. Walker, N. Colledge, S. Ralston & I. Penman, eds. *Davidson's Principle and Practice of Medicine*. 22nd ed. London: Elsevier. pp.921-87.

Friedman, L.S., 2017. Liver, Biliary Tract & Pancreas Disorders. In M.A. Papadakis, J. McPheem Stephen & M.W. Rabow, eds. *Current Medical Diagnosis and Treatment*. 56th ed. New York: Lange-McGraw Hill. pp.674-724.

Grimm, D., Thimme, R. & Blum, H., 2011. HBV life cycle and novel drug targets. *Hepatol Int*, 5, pp.644-53.

Liaw, Y.F. & Chu, C.M., 2009. Hepatitis B Virus Infection. *The Lancet*, 373, pp.582-92.

Lok, A., 2015. *Clinical manifestations and natural history of hepatitis B virus infection*. [Online] Wolters Kluwer Available at: www.uptodate.com

Lok, A. & Negro, F., 2011. Hepatitis B and D. In E. Schiff, W. Maddrey & M. Sorrel, eds. *Schiff's Disease of the Liver*. 11th ed. UK: Wiley-Blackwell. pp.537-81.

Lok, Anna. 2017. Tenofovir for the treatment of adults with chronic HBV infection. Wolters Kluwer

Terrault, N.A. et al., 2015. AASLD Guidelines for Treatment of Chronic Hepatitis B. *Hepatology*.

Theise, N.D., 2015. Liver and Gallbladder. In V. Kumar, A.K. Abbas & J.C. Aster, eds. *Robbins and Cotran Pathologic Basis of Disease*. 9th ed. Philadephia: Alsevier Saunders. pp.821-39.

WHO, 2015. *Guideline For The Prevention, Care and Treatment of Persons with Chronic Hepatitis B infection*. [Online] WHO Available at: www.who.int